Following entry of this Amendment, claims 37-39, 42-49, 52-57 and 59-62 and 64-65 will be pending. Claims 60 and 63 have been canceled.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-39, 42-49, 52-57 and 59-65 stand rejected under 35 U.S.C. §112, first ¶, as lacking enablement.

The Examiner states that the claimed treatment is ineffective. The Examiner reasons that : (i) the Fletcher Declaration is not persuasive because the results of the Myloral trial do not rule out the possibility that the effects of the drug on autoimmune disease are due to placebo alone, (i.e., that clinical results for placebo were better than for the drug, and therefore the drug is ineffective because "**if a drug is not better than placebo, it is not effective;**" O.A. at p.3); (ii) the results using beta interferon were not persuasive because the claims do not positively recite another active ingredient, and Myloral has **no usefulness by itself** (O.A. at p.4); (iii) when Myloral was administered alone, the difference between drug and placebo was **not statistically significant**" (O.A. at p.3); (iv) as a result of the discrepancy in result between the human trials and the animal studies, the EAE and NOD **animal models are not reasonably predictive** of human response to bystander antigens (O.A. at p.4); (v) the NOD mouse is **not predictive of human therapy** using bystanders because it has only been shown to be predictive of the effectiveness of other immunosuppressive agents (as evidenced in Bach) which are not

being claimed (O.A. at p.4 and p. 5); (vi) the evidence in the specification is not directed to treatment of diabetes but to treatment of insulitis (O.A. at p.4); (vii) Mueller (a reference directed to anergy induction) is invoked to show **unpredictability** of the claimed bystander tolerization regime (O.A. at p.5); (viii) the arguments about effectiveness in suppressing autoimmune response are not applicable to the claims because only the early stages of diabetes are autoimmune and the claims are not limited to early diabetes (O.A. at p. 5); (ix) the treatments of Bach are not effective after three months of age, and the claims are not limited to three months or less (O.A. at p.6); (x) evidence of use of insulin peptide in the treatment of diabetes is not persuasive because the claims exclude insulin (O.A. at p.6), similarly, evidence of the use of autoantigens is not persuasive because the claims exclude autoantigens (O.A. at p. 7).

Applicants respectfully disagree with the Examiner's reasoning and conclusions for the reasons outlined below.

The Examiner's reasons can be divided into categories: the first category is underlied by the Examiner's apparent belief that effectiveness for patent purposes must be nothing short of a benefit statistically significantly better than control in a double-blind, controlled, phase-three type, clinical trial. The second category is defined by the Examiner's belief that the only acceptable evidence is evidence surgically designed to be directed to the claim, and that more general evidence that enables a person of skill in the art to make certain inferences about the claimed subject matter is unacceptable, and should be dismissed.

It is submitted that while these stringent standards of review may be appropriate for the U.S. Food & Drug Administration or for conclusions printed in rigorously peer-reviewed scientific journals, it is not the standard before the USPTO. Furthermore, it is submitted that as a result of the excess rigor, the foregoing requirements contravene the provisions of MPEP 2107-2107.02, especially those at page 2100-43.

In particular, the requirement that a drug must be shown to be better than placebo appears to be contrary to the MPEP precepts of requiring only a "practical utility" having "real-world value" articulated in MPEP 2107 at page 2100-31 of the July 1998 edition. Similarly, the emphasis placed on "usefulness" smacks of a utility-type rejection, such as is proscribed by MPEP § 2107-2107.02. The same is true of the remarks that the benefit between drug and placebo was not statistically significant, or that animal models are not reasonably predictive. Although the MPEP guidelines have been formulated with specific reference to utility rejections, the MPEP is very careful to provide that rejections under 35 U.S.C. § 112, first paragraph are supposed to address matters other than those related to the questions of whether or not an invention lacks utility. MPEP 2107 at page 2100-35 left column, first whole paragraph.

Additionally, the MPEP provides that data from in vitro or animal testing are generally sufficient to support therapeutic utility. In providing so, the MPEP recognizes that clinical trials should not be necessary, and that clinical trials can fail for reasons independent of the value or utility of the claimed invention.

Most important, the foregoing sections of the MPEP nowhere provide that the Examiner is to look for possible cracks in the applicants' evidence or should require the information in the specification and claims to pass very stringent test in order to be probative and supportive of the claims. Nowhere does the MPEP require that the Examiner scrutinize the evidence in order to discover possible reasons to reject applicants' claims.

To the contrary, the general claimant of the MPEP is supportive of granting patents for inventions. Case law in the MPEP explicitly rejects the requirement for statical significance of clinical data. MPEP 2107.01, page 2100-41 and Nelson v. Bowler, 626 F.2d, 853, 856-857 (CCPA 1980). All that is required is a satisfactory correlation between the effect on the animal and that expected in human beings. Here, applicants have provided evidence that reasonably supports the claims, and especially the validity of the principle of the claimed immunological treatment.

Turning to the second category of objections by the Examiner, applicants observe that the Examiner has apparently misunderstood the purpose for which the objected to evidence was provided. Accordingly, the Examiner's remarks will be addressed in detail below.

Applicants have provided more than the usual amount of evidence in support of the compliance of the present claims with Section 112. The evidence included the Fletcher declaration which gave a perfectly plausible explanation why the Phase III trial did not demonstrate a statistically significant different between myloral and placebo. The

evidence also included general evidence supportive of the fact that the animal models are considered to be good predictors of human therapies, and that they have successfully predicted the applicability to humans of immunomodulatory therapies, a class of therapies of which the claimed invention is a member.

The Examiner's reasons for discarding this evidence are, more often that not, unjustified as will be shown below:

Applicants originally provided the Fletcher declaration, in order to show that factors other than the ineffectiveness of the claimed treatment are likely responsible for the failure of a clinical trial to achieve statistical significance. However, contrary to the Examiner's assertion, the Fletcher declaration and exhibits nowhere indicate that placebo was better than the drug. Accordingly, there is absolutely no basis for that statement made by the Examiner at page 3 of the Office Action. Additionally, when Dr. Fletcher said that as between (i) the placebo patients who were on interferon and (ii) the Myloral patients who were on interferon, the benefit of the invention was more clearly defined, the Examiner dismissed these statements and rejected this evidence stating that the claims do not recite interferon. But this is not why the evidence was proffered. Rather, it was proffered to show that a deeper analysis of the results shows a clinical benefit in patients, and to lend additional support to Dr. Fletcher's explanation of the augmented placebo effect. Furthermore, the concomitant administration of interferon, which was also given to the placebo patients, is not excluded by the claims, since the claims recite "comprising" which is open-ended language. All of these reasons militate against the Examiner's dismissal of

the Fletcher declaration. The Examiner's refusal to consider the Fletcher declaration even for the limited purpose of providing an explanation is error.

The Examiner concluded that the Fletcher declaration is inconsistent with the animal studies because the clinical trial did not show a benefit to the patients as clearly as the animal studies show the benefit to the animals. From this the Examiner concludes that the animal model is totally unreliable and cannot be considered in determining enablement of the invention. It is respectfully submitted that the Examiner has not provided an appropriate basis for disagreeing with applicant's expert, and the Examiner has not provided a declaration similar to that of applicants' expert. Finally, the statement about inconsistency between the animal model and the clinical trial are totally unsupported. Had the Examiner objectively attempted to reconcile them, the Examiner would have had to accept the explanation of Fletcher as a likely explanation.

As to the reliability of the animal model, the Examiner has not provided any evidence disputing such reliability other than the fact that a clinical trial did not provide as good results in humans as had been observed in animals. However, this not the type of evidence that can destroy the reliability of an animal model, especially in as good and well-studied a model as the NOD mouse. Applicants have adduced a multitude of evidence which showed that the animal model in different situations was in fact a good predictor of the ultimate human therapy. Applicants never said that the global immunosuppression agents were the same as the bystander suppressor agents of the claimed invention. The animal models showed that a certain immunomodulatory regime would work in animals,

and the same regime was found later to work in humans. This lends credibility to the model as a predictor of immunomodulatory approaches in general, and provides a positive reason for the Examiner's consideration of the proffered evidence rather than its dismissal. Not only should the Examiner not discard this evidence, but she should accept it for what it is worth, namely as an indication that immunomodulatory approaches, proven in the animal model, can work in humans.

The Examiner's reliance on Mueller and the laundry list of allegedly unpredictable factors determining the response to an antigen of the immune system of a mammal is entirely misplaced. The Mueller disclosure is confined to anergy induction. The entire Mueller article has little to do with the claimed invention. T-cell anergy, or intravenous tolerance, is an immunomodulatory approach that operates by a totally different mechanism than the active suppression induced by the mucosal administration of bystander antigens of the present claims. T-cell anergy is induced by parenteral, not mucosal, administration of high doses of only those antigens which are the target of an immune attack. Anergy induction is said to result in programmed cell death or apoptosis or in clonal deletion of the pathogenic T cells which are directed specifically against the target autoantigen. See page 50, right hand side, second full paragraph of Mueller, in which Mueller states:

> This model system has already demonstrated that intravenous immunization of animals with high doses of MBP can induce tolerance to self-myelin as a result of apoptosis (programmed cell death) of pathogenic T cells.

Therefore Mueller uses a different route of administration (intravenous, not mucosal) a different antigen (the target antigen, not a bystander) and a different mechanism of action (anergy, not active suppression) from the claimed invention. Indeed, it is an advantage of the present invention that it does not have to address the complicated issues and questions involved in anergy. For example, the present invention does not have to administer the very antigen to which the pathogenic T cells are directed. Bystander suppression elicits regulatory T cells that recognize a known antigen, namely the administered antigen. The T cells so elicited home in on the site of the attack because the administered antigen used to elicit to them is native to the tissue or organ under autoimmune attack. Once at the locus of such attack, the regulatory T cells secrete regulatory cytokines. The cytokines are non-specific themselves but because the regulatory T-cells home in to the locus of autoimmune attack, the suppression is confined to the area of abnormal autoimmune response. Thus, the method of the invention is much closer to the non-specific immunosuppressant regimes tested in the NOD mouse (except that it does not cause global immunosuppression) than the anergy regime of Mueller. Therefore, the Examiner must not rely on Mueller because the principle of immunomodulation of Mueller is completely different from that of the present invention, so different that Mueller can be said to be non-analogous art.

The foregoing description of bystander suppression is accurately based on the specification at page 9, lines 5-12 and at page 15, lines 17-23, and thus is in no need of further substantiation.

The Examiner interpreted applicants' statement that diabetes can be treated with immunosuppressive agents only during the autoimmune stage of the disease as somehow requiring further amendment and restriction of the claims. This is not the case. The claims are already limited to autoimmune disease. By definition, the final stages of diabetes, when the pancreatic beta cells have been destroyed, are no longer autoimmune. Thus the present claims do not apply to the final stages of diabetes.

The Examiner dismissed the Bach article which was submitted by applicants, not for the purposes stated by the Examiner, but to show that a great variety of immunomodulatory agents were tried in the NOD mouse. This raises the inference that the NOD mouse is a good model for testing new therapies against diabetes. Applicants never said that Bach directly supports the presently claimed method. Bach only supports the validity of the animal model as a testing ground for immunomodulatory therapies in diabetes. Because so many different therapies were first tried on the NOD mouse, must be considered a reliable model.

The Examiner went on to say that the instant specification shows only suppression or reduction in insulitis and fails to support prevention of diabetes. Again, applicants respectfully disagree with the Examiner. Insulitis always preceded diabetes. This is demonstrated by Knip, already of record and before the Examiner. See, e.g., the Abstract. Insulitis is inflammation of the pancreas. It follows, that if insulitis is prevented or delayed, its end stage, diabetes, will also be prevented or delayed. Hence, treatment of insulitis is treatment of diabetes.

The Examiner relied on Bach's teaching that anti-H2II monoclonal antibodies prevent the onset of insulin dependent diabetes when administered before the NOD animals are two or three months of age. The Examiner appears to require a similar limitation in the present claims. This is totally incorrect. First, the NOD mouse develops over time. When newborn, NOD mice do not have insulitis or diabetes. The treatment with antibodies, which is not the same as bystander antigens, might have been more effective at the earlier stages of the disease rather than the later stages of the disease. The end stage of the disease of course has no autoimmunity. It is accordingly submitted that the present claims to not need to be amended any further since they are already limited to autoimmune disease, and the end stages of diabetes are not autoimmune. Moreover, human beings, unlike NOD mice, may develop diabetes at different ages and during time periods longer than three months. Accordingly, it is ludicrous to require the claimed method to be limited to three months. In any event, the specification need not teach what is very well known. What is very well known in insulin-dependent, or Type I, diabetes is that the disease stops being autoimmune once the beta cells of the pancreas have been destroyed. However, even if 5-10% of the pancreatic cells remain, these are enough for the subject to have some pancreatic function and to have autoimmunity. Accordingly, even if the subject has 5-10% of its pancreatic beta cells left, the subject would still benefit from abatement of the remaining autoimmune response. Accordingly, all of the Examiner's comments about the period of time for treatment are misplaced.

The Examiner also uses Bach against the present claims by stating that of all of the treatments disclosed in table I of Bach only 5 were satisfactory to the author. Such comments are common in research and review papers and they cannot be taken as negating any redeeming value for claimed invention or for the treatments criticized by Bach. Immunology is full of apparent contradictions. If every statement in every publication were taken at full-face value, no patent would ever issue for any immunological invention.

The Examiner also dismisses the evidence provided by applicants involving the use of an insulin peptide in the treatment of diabetes or the use of autoantigens in the treatment of diabetes. This evidence was not submitted to support the claimed subject matter directly, but indirectly. Insulin is an antigen; its oral or mucosal administration is a form of oral tolerance, a regime that is close to bystander suppression. Similarly, autoantigens orally administered to tolerize against other immune disease are also probative of the value of other tolerizing immunomodulatory regimes, such as bystander suppression. Evidence involving insulin and autoantigen was offered for this purpose and not as direct support of the claimed subject matter.

In view of the above remarks, applicants respectfully request that the Examiner withdraw this rejection.

DOUBLE PATENTING REJECTIONS

Applicants repeat their intention to file appropriate terminal disclaimers over applications forming the basis for the provisional double-patenting rejections once there is an indication of allowability.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 60, 61, 63, and 64 were rejected on the basis that the term "substantially" is indefinite.

It is respectfully submitted that the phrase "substantially pure" or "substantially free" is commonly accepted in this art, as well as in this particular examining group, as being a definite way to claim a composition of matter.

Withdrawal of this rejection is respectfully requested.

The use of the term "substantially" in a claim does not make the claim vague or indefinite *per se*. Rather,

> its acceptability depends on 'whether one of ordinary skill in the art would understand what is claimed . . . in light of the specification', even if experimentation may be needed.

Andrew Corp. v Gabriel Electronics, Inc., 847 F.2d. 819, 821 (Fed. Cir. 1988) (holding that the phrase "substantially equal" was definite).

It is submitted that a person of skill in the art would understand that the term "substantially free of autoantigens" indicates that level of bystander antigen purity achieved

by using standard antigen purification techniques (specification, page 15, lines 21-22), which do not guarantee 100 % purity. In other words, a person of skill in the art would know at what level of purity a bystander antigen is "substantially free of autoantigens" and would be able to determine the scope of the invention as presently claimed. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, second ¶, is believed to be in order and is respectfully requested.

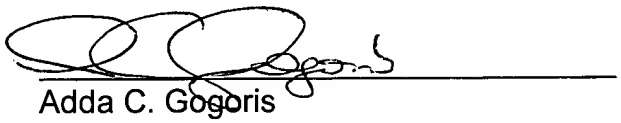
The foregoing is particularly applicable with respect to claims such as claim 61, which depends from claim 60 which recites "purified". Claim 61 merely makes clear that routine purification techniques can be used to rid a composition containing bystander antigen from autoantigens (albeit perhaps not completely).

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

It is submitted that the pending claims are now in condition for allowance. Issuance of a Notice to that effect is earnestly solicited.

Respectfully submitted,



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